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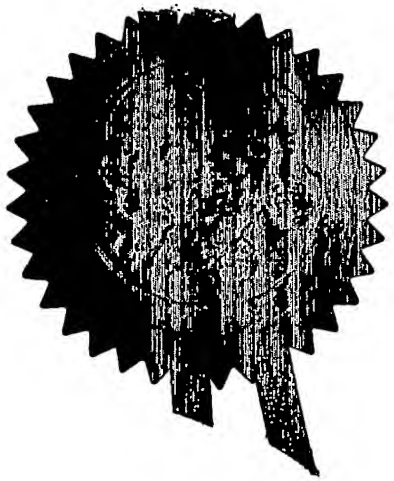

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Cardiff Road
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1. Your reference GBP88234

2. Patent application number
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3. Full name, address and postcode of the or of each applicant (underline all surnames)

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07262868004

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention NEW CYTOTOXIC DEPSIPEPTIDES

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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Country	Priority application No (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

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Description	19
Claim(s)	
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Request for substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature Marks & Clerk Date: 24 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Patent Chemical Formalities
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Document : 930682

NEW CYTOTOXIC DEPSIPEPTIDES

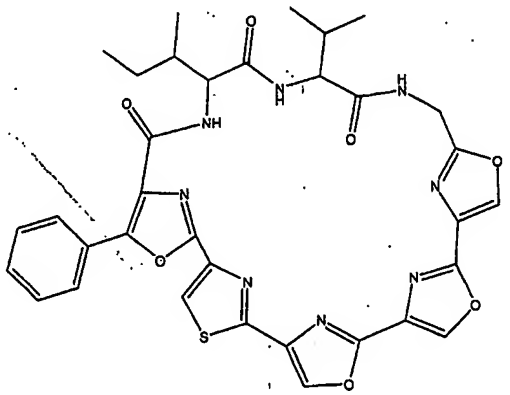
FIELD OF THE INVENTION

The present invention relates to new depsipeptide compounds, pharmaceutical compositions containing them and its use as an antitumoral agent.

BACKGROUND OF THE INVENTION

Several cyclic peptides obtained from marine organism have been disclosed (see for example Rudi A. et al., *J. Nat. Prod.*, 2003, 66, 575-577: "Didmolamide A and B, two new cyclic hexapeptides from the marine Ascidian *Didemnum molle*".

JP 11180997 discloses an antitumor compound of formula



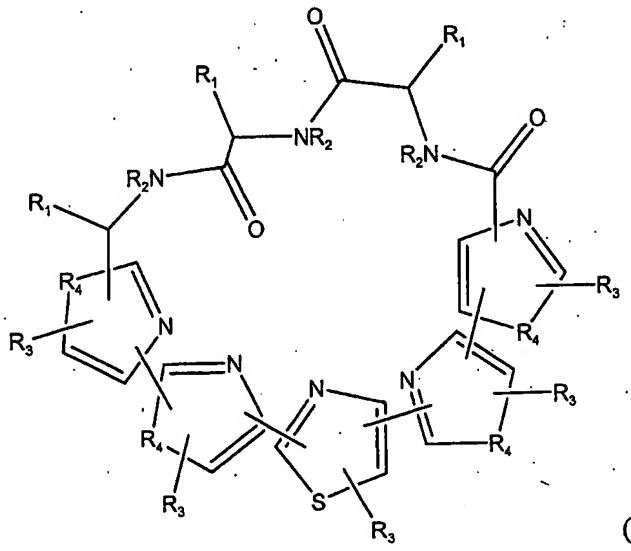
which is obtained from Streptomyces nobilis. Its IC_{50} in Hela S3 cells is 14 nM.

Cancer is a leading cause of death in animals and humans. Several efforts have been and are still being undertaken in order to obtain an antitumor agent active and safe to be administered to

patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that are useful in the treatment of cancer.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of general formula **I** or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof:



(I)

wherein

R_1 and R_3 groups are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, nitro, azido, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaromatic and substituted or unsubstituted acyl;

R_2 groups are each independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or

unsubstituted aryl, substituted or unsubstituted alkoxy and substituted or unsubstituted acyl;
R_4 groups are each independently selected from O and S.

The present invention also relates to the obtention of the compounds of formula **I**. In particular, the compound we call IB-01211 can be obtained from a strain of microorganism capable of producing it. The preferred process comprises the steps of cultivating a strain of microorganism capable of producing IB-01211 in an aqueous nutrient medium with assimilable carbon and nitrogen sources and salts, under controlled submerged aerobic conditions, and then recovering and purifying the compounds according to the invention from the cultured broth.

Other compounds of this invention can be derived from IB-01211, or can be made by synthesis. Thus, the oxazole/thiazole fragment of the compounds of the present invention can be synthesised by using the teaching of the following literature: Panek J. S. et al. "Studies directed toward the synthesis of Ulapualide A. Asymmetric Synthesis of the C8-C25 tris-oxazole fragment" J. Org. Chem. 1996, 61, 6496-6497; Panek J. S. et al. "Studies directed toward the total synthesis of kabiramide C: asymmetric synthesis of the C7-C19 fragment" Tetrahedron Lett. 1998, 39, 6143-6146; Panek J. S. et al. "Synthesis of the fully functionalized tris-oxazole fragment found in metabolites derived from marine organisms" Tetrahedron Lett. 1997, 38, 5445-5448; Pattenden G. "Synthetic studies with natural oxazoles and thiazoles" J. Heterocyclic Chem. 1992, 29, 607-618; Pattenden G. et al. "Synthesis of the tris-oxazole ring system of ulapualides" Synlett. 1990, 36-37; Kiso Y. et al. "Convergent synthesis of (-)-mirabazole C using a chloroimidazolidium coupling reagent, CIP" J. Org. Chem. 1996, 61, 3350-3357; Wipf P. et al. "Total synthesis of (-)-thiangazole and structurally related polyazoles" J. Org. Chem. 1995, 60, 7224-7229; Wipf P. et al. "A new synthesis of highly functionalised oxazoles" J. Org.

Chem. 1993, 58, 3604-3606. Once the oxazole/thiazole fragment is synthesised the aminoacidic fragment is introduced by using conventional methods of peptide synthesis already known by the skilled person in the art.

In another aspect, the present invention is directed to pharmaceutical compositions containing a compound of formula **I** or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof, together with a pharmaceutically acceptable carrier or diluent.

In another aspect, the present invention is also directed to the use of compounds of formula **I** or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof in the treatment of cancer, or in the preparation of a medicament for the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. HPLC/UV chromatogram and UV spectrum of purified IB-01211

Figure 2. IR spectrum of purified IB-01211

Figure 3. ^{1}H NMR spectrum of purified IB-01211

Figure 4. ^{13}C NMR spectrum of purified IB-01211

Figure 5. DEPT spectrum of purified IB-01211

Figure 6. COSY 45 spectrum of purified IB-01211

Figure 7. HMQC spectrum of purified IB-01211

Figure 8. HMBC spectrum of purified IB-01211

Figure 9. HPLC/MS chromatogram and ESI-MS spectrum of purified IB-01211

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of general formula **I** as defined above.

In these compounds the substituents can be selected in accordance with the following guidance:

Alkyl and alkoxy groups preferably have from 1 to 24 carbon atoms. One more preferred class of alkyl groups has 1 to about 12 carbon atoms, yet more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Another more preferred class of alkyl groups has 12 to about 24 carbon atoms, yet more preferably 12 to about 18 carbon atoms, and most preferably 13, 15 or 17 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more prefereably 2 to about 6 carbon atoms, even more prefereably 1, 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refere to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Suitable aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl

groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred aryl groups include substituted or unsubstituted phenyl, naphthyl, biphenyl, phenanthryl; and anthracyl.

Suitable acyl groups have from 2 to about 12 carbon atoms, more preferably from 2 to about 8 carbon atoms, still more preferably from 2 to about 6 carbon atoms, even more preferably 2 carbon atoms.

Suitable heterocyclic groups include heteroaromatic and heteroalicyclic groups. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl groups.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OH, OR', SH, SR', SOR', SO_2R', NO_2, NH_2, NHR', $N(R')_2$, NHCOR', $N(COR')_2$, $NHSO_2R'$, CN, halogen, C(=O)H, C(=O)R', CO_2H, CO_2R', OC(=O)R' wherein each of the R' groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, C(=O)H, $C(=O)CH_3$, CO_2H, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl.

Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

The term "pharmaceutically acceptable salts, derivatives, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs and derivatives can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylenethanolamine, triethanolamine and basic aminoacids salts.

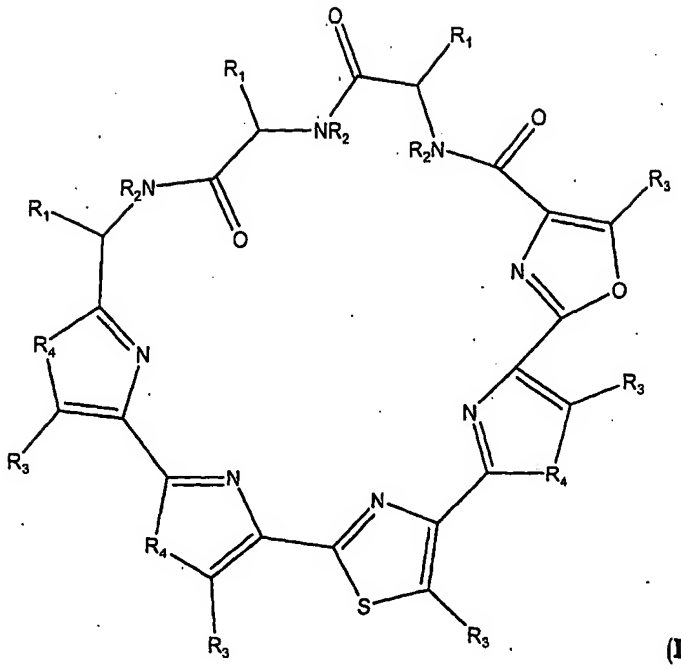
The compounds of the invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that

both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Any compound that is a prodrug of a compound of formula **I** is within the scope and spirit of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative.

The compounds of the present invention represented by the above described formula **I** may include enantiomers depending on their asymmetry or diastereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

Preferred compounds of the invention are those of general formula **II**

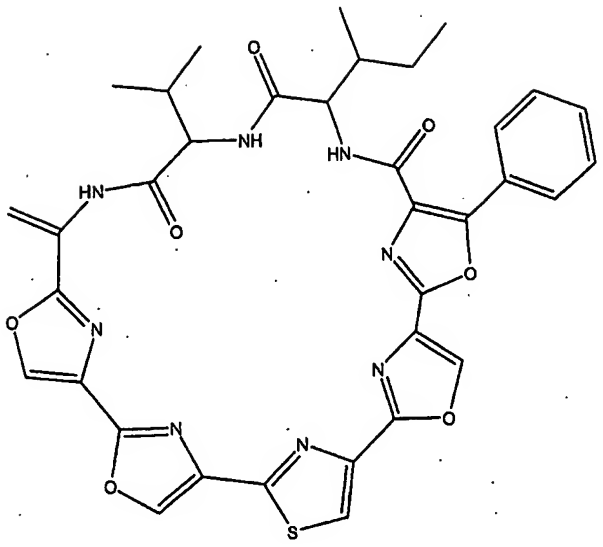


(II)

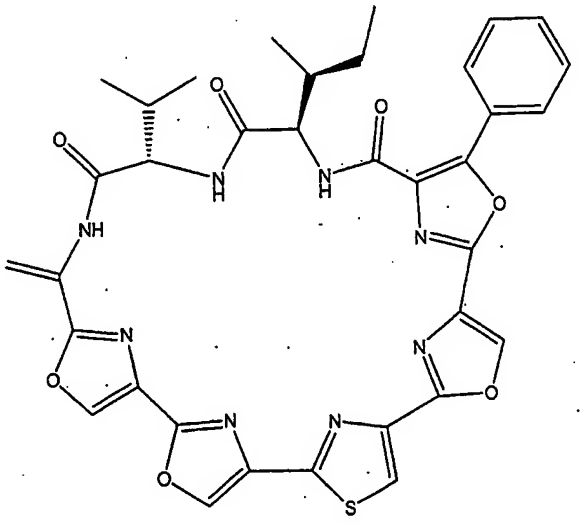
wherein R_1, R_2, R_3 and R_4 groups have the same meaning as defined above.

Preferred R_1 groups are substituted or unsubstituted alkyl and substituted or unsubstituted alkenyl, more preferred are substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted C_1-C_6 alkenyl, still more preferred are isopropyl, 2-methylbutyl and methylene. Preferred R_2 groups are H and substituted or unsubstituted alkyl, and more preferred is H. Preferred R_3 groups are H and phenyl. Preferred R_4 groups is O.

One particularly preferred compound of formula **I** is compound IB-01211:



The preferred stereochemistry of the above mentioned compound is the following



An important feature of the above described compounds is its bioactivity and in particular its cytotoxic activity. With this invention we provide novel pharmaceutical compositions of these compounds that possess cytotoxic activity, and its use as antitumor agents. Thus the present invention further provides pharmaceutical compositions comprising a compound of this invention or a pharmaceutically

acceptable salt, derivative, prodrug or stereoisomer thereof with a pharmaceutically acceptable carrier.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) suitable composition for oral, topical or parenteral administration.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of the invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

Compound IB-01211 is preferably obtained from an actinomycete, named strain ES7-008. A culture of this strain has been deposited in the Colección Española de Cultivos Tipo at the University of Valencia, in Spain, under the accession number CECT 3358. This deposit has been made under the provisions of the Budapest Treaty.

ES7-008 produces compound IB-01211 when it is cultured under controlled conditions in a suitable medium. This strain is preferably grown in an aqueous nutrient medium, under aerobic and mesophilic conditions, preferably at 28°C-40°C and at a pH ranging between 6.0 and 8.0. A wide variety of liquid culture media can be used for the cultivation of the organism. Useful media are those that include an assimilable carbon source, such as starch, dextrin, sugar molasses, glucose, an assimilable nitrogen source such as protein, hydrolysed protein, defatted meals, corn steep, and useful inorganic anions and cations such a sodium, magnesium, potassium, ammonium, sulfate, chloride, phosphate, carbonate. Trace elements may be added also. Aeration is preferably achieved by supplying air to the fermentation medium. Agitation is provided by a mechanical impeller. Conventional fermentation tanks have been found to be well suited for carrying out the cultivation of this organism. The addition of nutrients and pH control as well as antifoaming agents during the different stages of fermentation may be needed for increasing production and avoid foaming.

Compound IB-01211 can be produced starting with a frozen lyophilized mycelium of ES7-008. A mycelial mass is obtained by culturing the initial cells in shake flasks with a culture medium containing some of the ingredients described above at mesophilic temperatures and in aerobic conditions. This step may be repeated several times as needed and the material collected will be used as an inoculum to seed one or several fermentation tanks with the appropriate culture medium. If it is desired these tanks can be used for

developing the inoculum or for the production stage, depending on the broth volume needed. Sometimes the production medium may be different than the ones used for inoculum development. In Table 1, it is disclosed typical media that can be used for inoculum development and for production of IB-01211.

TABLE 1

Inoculum medium			**Production medium**	
Soybean flour	5 g		Yeast	5 g
Glucose	1 g		Peptone	1 g
Starch	24 g		Soybean flour	3 g
Beef extract	3 g		Soybean meal	15 g
Yeast extract	5 g		Yeast extract	5 g
Tryptone	5 g		Tryptone	2 g
$CaCO_3$	4 g		$CaCO_3$	4 g
NaCl	5 g		NaCl	4 g
Na_2SO_4	7 g		Na_2SO_4	1 g
KCl	0.2 g		KCl	0.5 g
$MgCl_2$	2 g		$MgCl_2$	2 g
H_2O	To 1 liter		K_2HPO_4	0.5 g
			H_2O	To 1 liter

Compound IB-01211 can be isolated from the mycelial cake by extraction with a suitable mixture of solvents such as $CHCl_3$:CH_3OH:H_2O. The activity is concentrated in the lower layer. The extracts from two repeated extraction can be combined and evaporated to dryness *in vacuo*.

Separation and purification of IB-01211 from the crude active extract can be performed using the proper combination of conventional chromatographic techniques.

Fractionation can be guided by the antitumor activity of fractions, by TLC visualized with vanillin in concentrated H_2SO_4 or by analytical

HPLC with photodiode-array and MS detector. HPLC analysis is performed at room temperature using an analytical column Symmetry C18 (5μ) and a MeOH:H_2O:HOAc 95:5:1 mobile phase at a flow rate of 0.3 ml/min and plotted at 260 nm. In this conditions IB-01211 retention time is 5.1 min as it is shown in Fig.9.

EXAMPLES

Example 1: Production of IB-01211

Inoculum development: a frozen culture of ES7-008 or a well grown slant culture (5% vol.) is used to seed 100 ml of a seed medium, as described in Table 1, that it is contained in a 250 ml shake flask. The flask is incubated during 48 h. A 2 l Erlenmeyer flask with 500 ml of the same medium is seeded with 10% vol. of the first stage inoculum. The flask is incubated during 48h.

Fermentation step: 50 l of production medium, as described in Table 1, contained in a 75 l fermentation tank are seeded with 2.5 l of second stage inoculum. The fermentation is carried out during 96 h with 400 rpm agitation and an air flow of 0.5V/V.M.

Example 2: Isolation of IB-01211

8.5 liters of whole harvested broth were filtrated to separate the biomass and other solids. The mycelia cake was extracted twice with a mixture solvent (2.4 l) of $CHCl_3$:CH_3OH:H_2O (2:1:1). The activity was concentrated in the lower layer. The organic solvent was concentrated and evaporated to dryness *in vacuo* to yield 4.8 g of crude extract.

The extract was applied to a silica gel VFC (vacuum flash chromatography) system, using a mixture of n-hexane-EtOAc and EtOAc-MeOH as eluting solvents. The fractions with antitumor activity, containing IB-01211 (900 mg) were eluted with EtOAc-MeOH 1:1, EtOAc-MeOH 1:3 and methanol. The active fractions were chromatographied

twice with a silica gel column using $CHCl_3$-MeOH and EtOAc-MeOH mixtures as eluting solvents. The cytotoxic activity was detected in fractions eluted with $CHCl_3$-MeOH 96:4 in the first chromatography (200 mg of pure compound IB-01211) and in fractions eluted with EtOAc-MeOH 85:15-8:2 in the second chromatography (60 mg of pure compound IB-01211). Further purification with C18 reversed phase chromatography afforded 22 mg of pure compound IB-01211 eluted with MeOH.

On the basis of detailed analysis of their various spectral characteristics, the pure compound can be identified as IB-01211. The UV spectrum shows absorption at 225 nm, 265 nm and 290 nm as reported in Fig. 1. The infrared absorption spectrum is shown in Fig. 2 of the accompanying drawings. The ^1H NMR, ^{13}C NMR and DEPT spectra of IB-01211 are reported in Fig.3, Fig.4 and Fig. 5, respectively. The 2D NMR experiments COSY, HMQC and HMBC are reported in Fig. 6, Fig. 7 and Fig. 8, respectively. The ES-MS spectrum of IB-01211 displays a (M+Na) peak at 731 as reported in Fig. 9. ^1H and ^{13}C NMR data of compound IB-01211 are summarized in Table 2.

TABLE 2

Position	^{13}C (δ)	^1H (δ)	Position	^{13}C (δ)	^1H (δ)
Isoleucine			Oxazole (2)		
NH		8.46 (d, 10.6)	2-C	156.1	
αCH	57.3	4.99 (dd, 10.5, 4.4)	4-C	136.4	
βCH	37.8	2.23 (m)	5-CH	136.9	8.16 (s)
γCH_2	26.6	1.41 (q, 7.5)			
		1.20 (m)			
γCH_3	14.9	1.05 (d, 6.9))	Thiazole		
δCH_3	11.9	0.87 (t, 7.2)	2-C	157.8	
CO	173.3		4-C	142.2	
			5-CH	119.1	7.90 (s)
Valine					
NH		7.37 (d, 5.4)	Oxazole (3)		

αCH	63.6	4.06 (dd, 8.7, 5.6)	2-C	158.6	
βCH	30.2	2.21 (m)	4-C	130.6	
γCH_3	19.5	0.95 (d, 6.8)	5-CH	137.4	8.27 (s)
γCH_3	20.0	0.99 (d, 6.8)			
CO	171.2		Oxazole (4)		
			2-C	152.0	
Oxazole (1)			4-C	129.8	
NH		8.28 (bs)	5-C	153.6	
αC	127.5		1'-C	126.8	
βCH_2	106.8	6.50 (s)	2',6'-CH	128.3	8.42 (dd, 7.0, 1.2)
		5.88 (s)	3',5'-CH	128.8	7.49 (m)
2-C	159.9		4'-CH	130.7	7.47 (m)
4-C	130.3		CO	161.2	
5-CH	139.1	8.2 (s)			

Example 3: Biological activity

BIOASSAYS FOR ANTITUMOR SCREENING

The finality of these assays is to interrupt the growth of a "in vitro" tumor cell culture by means a continued exhibition of the cells to the sample to be testing.

CELL LINES

Name	N° ATCC	Species	Tissue	Characteristics
K-562	CCL-243	human	leukemia	erythroleukemia (pleural effusion)
A-549	CCL-185	human	lung	lung carcinoma "NSCL"
SK-MEL-28	HTB-72	human	melanoma	malignant melanoma
HT-29	HTB-38	human	colon	colon adenocarcinoma
DU-145	HTB-81	human	prostate	prostate carcinoma, not androgen receptors
LNCaP	CRL-1740	human	prostate	prostate adenocarcinoma, with androgen receptors
PC-3		human	prostate	prostate adenocarcinoma
BT-474		human	breast	breast adenocarcinoma
MX-1		human	breast	breast adenocarcinoma,
Hs746t		human	gastric	
SK-HEP-1		human	liver	
SK-OV-3	HTB-77	human	ovary	ovary adenocarcinoma (malignant ascites)
PANC-1	CRL-1469	human	pancreas	pancreatic epitheloid carcinoma
5637		human	bladder	
FADU		human	pharynx	
786-O		human	renal	
NCI-H187		human	SCL	
Y-79		human	retinoblastoma	
SW694		human	fibrosarcoma	
CHSA		human	chondrosarcoma	
OSA-FH		human	osteosarcoma	
SK-N-MC		human	neuroblastoma	
TT		human	thyroid	
SW-579		human	thyroid	
HL-60		human	promyelocytic leukemia	
H9		human	lymphoma	
MC116		human	lymphoma	

INHIBITION OF CELL GROWTH BY COUNTING CELLS

Tetrazolium Assay MTS is based on metabolic reduction of MTS to solubilized formazan crystals by the metabolically active mitochondria of living cells. For this reason, the methodology will include counting of the cell lines based on viability staining to ensure that cell concentrations are corrected to allow for 100% living cells into each well in lieu of Coulter counting or estimated dilutions based on standard growth curves.

Medium containing drug was removed at the end of the treatment and culture plates rinsed one time with PBS. Afterward, cells were incubated in 200 µl of drug-free medium until 72 hours. After appropriate incubation time 25 µl of MTS+PMS solution was added to each microtiter well and incubated for 4 hours at 37C. Plates were then removed from the incubator and placed on plate shaker for 5 minutes (covered for protection from light). Optical densities were read at 490nm on spectrophotometer plate reader. Data was analyzed using Softmax.

Data is presented as IC_{50} potencies calculated from 3rd order polynomial regression curves using Microsoft Excel and then manually interpolated.

Table 3 illustrates data on the biological activity of the compounds of the present invention.

Table 3. Citotoxic activity (mol/l)

	Bladder	Breast		Colon	Gastric	Liver	NSCL	Ovary	Pancreas	Pharynx	Renal
	5637	BT-474	MX-1	HT-29	Hs746t	SK-HEP-1	A549	SK-OV-3	PANC-1	FADU	786-O
IC_{50}	3.39E-7	5.37E-7	8.62E-7	8.17E-7	6.92E-7	6.64E-7	9.18E-7	9.46E-7	4.24E-7	6.64E-7	6.92E-7

	Prostate			SLC	Retinoblastoma	Melanoma	Fibrosarcoma	Chondrosarcoma
	PC-3	DU-145	LNCAP	NCI-H187	Y-79	Mel-28	SW 694	CHSA
IC_{50}	6.21E-7	4.8E-7	6.5E-7	2.97E-8	9.32E-8	5.08E-7	7.2E-7	3.53E-7

	Leukemias/Lymphomas				Osteosarcoma	Neuroblastoma	Thyroid	
	HL-60	K562	H9	MC116	OSA-FH	SK-N-MC	TT	SW-579
IC_{50}	1.41E-7	6.36E-7	1.84E-7	3.39E-6	7.2E-7	5.37E-7	4.38E-6	4.52E-7